REMARKS

Claims 12-16, 18-24, 26-27, 33-35 and 41-43 have been amended, without prejudice or disclaimer. Claims 1-11, 17, 25, 28-32 and 36-40 are canceled, without prejudice or disclaimer. Claims 36-40 were canceled as being redundant in view of the claim amendments made herein. Support for the amendments to claims 12-16, 18-24, 26-27, 33-35 and 41-43 can be found, *e.g.*, in paragraphs 21, 30 and 33-35 of the present application. No new matter has been added.

The claim amendments and cancellations made herein are for the purpose of expediting prosecution of the instant application. Applicants do not acquiesce to the rejections made by the Office, and reserve the right to pursue the canceled subject matter in one or more continuing applications.

Applicants note with appreciation the Office's reconsideration and withdrawal of certain claim rejections. To the extent that the Office maintains one or more of the rejections discussed below after the present claim amendments are entered and considered, Applicants request a telephonic interview with the Examiner to discuss these rejections.

Sequence Compliance

In order to perfect sequence compliance according to paragraph 8 of the Office Action, Applicants submit that no new matter was added to the specification by the paper copy of the computer readable form of Sequence Listing submitted on October 3, 2007.

Claim Objections

Claim 20 is objected to in the recitation of "the amino acid sequence of residues 58-447 of SEQ ID NO:1...the backbone atoms of said amino acids" and claims 21-22, is objected to in the recitation of "said amino acids..." Applicants have amended the pending claims to recite consistent terminology, such as "the amino acid sequence of residues" or "amino acid residues" throughout.

The objection of the claims for not reciting the appropriate sequence identifier is moot in view of the amendments made herein to include "SEQ ID NO:3" when referring to the APP peptide inhibitor in the claims.

Reconsideration and withdrawal of these claim objections is respectfully requested.

Rejection of Claims 12-16, 18-24, 26-27, and 33-43 under 35 U.S.C. §112, Second Paragraph

In paragraphs 11a-b, the Office has rejected claims 12-16, 18-24, 26-27, and 33-43 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In one aspect of the rejection, the Office alleges that Claims 12 (claims 13-16, 18-19,33, 35, 37,40, and 42-43 dependent therefrom) and 20 (claims 21-24, 26-27, 34, 36, 38-39, and 41 dependent therefrom), prior to the present amendment, are unclear in their recitation of "providing a three dimensional structure..." followed by the step of "generating a three dimensional model..." In particular, the Office requests clarification with respect to "how "a three dimensional structure" is distinct from "a three dimensional model," as one of skill in the art would recognize the two phrases as being essentially synonymous."

Without prejudice or disclaimer, the particular terms objected to by the Office have been changed by the claim amendments made herein. As presently pending, the claims are directed, *inter alia*, to methods of identifying candidate agents that interact with the APP binding site of BACE by using the three-dimensional structural coordinates of a particular BACE:APP inhibitor complex to generate a three-dimensional representation of the complex; identifying particular amino acid residues in the APP-binding site of BACE that form the APP-binding site of the BACE peptide to form a three-dimensional model of the APP-binding site comprising selected BACE amino acid residues; and employing said three-dimensional representation to identify the candidate agent. Thus, the claims, as pending, require the use of a three-dimensional representation of the particular structural coordinates of the BACE:APP inhibitor complex disclosed in the present application, followed by an evaluation of the three-dimensional model of the APP-binding site of BACE based on the three-dimensional representation of the complex. Applicants agree with the Office's position that the terms "three-dimensional model" and "three-dimensional representation" are essentially synonymous, and that one of ordinary skill in the art would consider these terms to be of similar scope. These terms are being used to mirror the language in the specification in, *e.g.*, paragraphs 21 and 33-35 of the specification, and to simply distinguish between the initial three-dimensional representation of the complex of BACE:APP inhibitor from which the amino acid residues located in the APP-binding site of BACE were

identified. If even in view of this explanation, the Office maintains the position that the terms are unclear, Applicants invite the Examiner to suggest alternative language.

In another aspect of this rejection, the Office has rejected Claims 42-43 as being allegedly confusing "as it is unclear as to how the additional method step of "providing a crystalline composition of BACE" is intended to be incorporated into the method of claim 12." This rejection has been met by amending the rejected claims to recite that the three-dimensional structural coordinates of the complex of the BACE peptide and the APP inhibitor were obtained by subjecting a co-crystal comprising the BACE peptide in complex with the APP inhibitor to X-ray diffraction and collecting data sufficient to determine the three-dimensional coordinates of said complex. Thus, the order of the steps and the relationship between the BACE:APP inhibitor co-crystal and the three-dimensional structural coordinates are clarified.

Accordingly, reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, second paragraph, is respectfully requested.

Rejection of Claims 12-15, 20-23, and 37-39 under 35 U.S.C. §101

In paragraph 12 of the Office Action, claims 12-15, 20-23, and 37-39 were rejected under 35 U.S.C. §101 because the claimed methods allegedly do not "transform" the data to a "different state or thing" as no active selection or screening step is identified by the claims.

This rejection has been met by amending the pending method claims to require the steps of obtaining or synthesizing the candidate agent and/or contacting in vitro or in vivo the candidate agent with BACE identify agents that bind, interact, or alter the activity of BACE. Thus, the pending claims, as amended herein, require at least one concrete active step.

Reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §101 is respectfully requested.

Rejection of Claims 12-16, 18-24, 26-27, and 33-36 under 35 U.S.C. §112, First Paragraph

Written Description

The Office has rejected claims 12-16, 18-24, 26-27, and 33-36 under 35 U.S.C. §112, first paragraph, for alleged lack of written description by maintaining "the position that the specification fails to adequately describe the genus of 3-D models as encompassed by the claims." According to the Office:

> There is no dispute that claim 12 (and claims dependent therefrom) specifies the that the BACE comprises residues 58-447 of SEQ ID NO:1, the APP inhibitor comprises SEVNStaVAEF, and the 3-D structure comprises the structure coordinates of those recited amino acids according to Figures 1A-1EEE ("Figure 1"). Also, there is no dispute that claim 20 (and claims dependent therefrom) specifies the that the BACE "consists essentially of' residues 58-447 of SEQ ID NO:1 and the 3-D model of BACE has the structural coordinates of Figure 1. (Office Action, pages 7-8)

However, the Office has taken the position that since claim 12 as presented previously recited the transitional phrase "comprises" in part (iii) of claim 12, "the genus of 3-D structures encompasses additional amino acid sequence according to "residues 58-447 of SEQ ID NO:1, wherein the 3-D position(s) of the additional amino acids are undefined, and thus the genus of 3-D structures used in the claimed method encompasses homology models." In addition, the Office takes issue of the fact that the 3-D positioning of the APP inhibitor, which is an essential element of the 3-D model, is unlimited in the claims."

To expedite prosecution of the present application, Applicants have amended the pending method claims to require the use of the three-dimensional coordinates of the complex of BACE:APP inhibitor according to Figures 1A-1EEE within the deviation specified. In view of the Office's maintained position (with which Applicants disagree), the claims have been further amended to recite the transitional phrase "consisting essentially of" when referring to the amino acid sequences of the BACE peptide and the APP inhibitor. It is noted for the record that the human BACE peptide amino acid sequence recited in the claims as amended herein may contain additional non-BACE elements that do not materially affect the basic and novel characteristics of the claims. Thus, the Office's rejection has been met.

Applicants note with appreciation the Office's reconsideration and withdrawal of certain aspects of the written description rejection stated in the previous Office Action. However, on pages 8-12 of the Office Action, the Office appears to maintain the position that the claims, prior to the present amendments, encompass "homology modeling" as defined by the Office and unpredictable crystallization conditions primarily in view of the "unlimited" transitional phrase when referring to the BACE amino acid sequence in claim 12 and/or the ligands. As stated above, this rejection has been met by the present amendments. To the extent that the Office considers that the present claim amendments do not meet the present rejection, Applicants reiterate the position stated on pages 13-18 of the Amendment filed on October 3, 2007. In

essence, the description in Flower ("Drug Design, Cutting Edge Approaches," Royal Society of Chemistry, Cambridge, UK, 2002) referred to three-dimensional models generated for a protein for which no specific three-dimensional structure was available, but the three-dimensional structure available was based on a homologous protein. This is not the case here as the claims are directed to screening methods that are based on the three-dimensional structural coordinates of the particular BACE:APP inhibitor complex within the particular deviation specified. Thus, as stated in the previous Office Action, homology modeling, without the benefit of the solved structure as described in Flower, is not relevant to the present claims. Applicants' position is consistent with Lambert *et al.*, US 2004/0137518, which provides in the passage alluded to by the Office the following:

> [0017] The solved PPARalpha-ligand crystal structure would provide structural details and insights necessary to design a modulator of PPARalpha that maximizes preferred requirements for any modulator, i.e. potency and specificity. ***By exploiting the structural details obtained from a PPAR-ligand crystal structure, it would be possible to design a PPAR modulator that, despite PPARalpha's similarity with other PPARs, exploits the unique structural features of PPARalpha. A PPAR modulator developed using structure-assisted design would take advantage of heretofore unknown PPAR structural considerations and thus be more effective than a modulator developed using homology-based design.*** Potential or existent homology models cannot provide the necessary degree of specificity. A PPAR modulator designed using the structural coordinates of a crystalline form of PPARalpha would also provide a starting point for the development of modulators of other PPARs. (US 2004/0137518, emphasis added)

The above-quoted paragraph underscores the advantages of having the solved crystal structure of, in this case, PPARalpha, compared to homology-based design without the benefit of the solved structure. Accordingly, the above-quoted passage actually supports Applicants' position that the structural details obtained through the three-dimensional coordinates of BACE set forth in Figures 1A-1EEE allows the skilled artisan to design or identify a candidate agent "more effective than a modulator developed using homology-based design." *Id.*

Similarly, Applicants reiterate the position above that the Office's arguments regarding the unpredictability of crystallization conditions are not relevant to the claims, as amended herein, since the claims specify the three-dimensional structural coordinates of the complex of the particular BACE peptide and APP inhibitor, and the particular crystal space group and unit cell parameters (see e.g., claims 42-43).

The Office maintains the position of the unpredictability of the art of homology models and crystallization conditions. Without making any admissions or acquiescing to the Office's positions, Applicants will not continue to address the specifics of the Office's position in this regard as it is not relevant to the present claims.

In view of the above, reconsideration and withdrawal of the present rejection is respectfully requested.

Enablement

On pages 13-21 of the Office Action, the Office has rejected the pending claims for alleged lack of enablement. Since several grounds for this rejection parallel the written description rejection discussed above, Applicants reiterate the position above that the Office's rejection has been met by amending the claims to require the use of the three-dimensional coordinates of the complex of BACE:APP inhibitor according to Figures 1A-1EEE within the deviation specified. The claims have been further amended to recite the transitional phrase "consisting essentially of" when referring to the amino acid sequences of the BACE peptide and the APP inhibitor. Moreover, claims 12 and 20 have been amended to replace the phrase "providing a three-dimensional structure," which was objected to by the Office as being "intended as encompassing crystallizing a polypeptide to obtain (or provide) the structural coordinates of the crystallized polypeptide." (Office Action, page 14). As amended herein, claims 12 and 20 now recite the step of "utilizing the relative three-dimensional structural coordinates of a complex of a BACE peptide and an APP inhibitor according to Figures 1A-1EEE, ± a root mean square deviation from the backbone atoms of the amino acid residues in the complex not more than 1.5Å, to generate a three-dimensional representation of the complex."

In view of the claim amendments made herein and Applicants clarification that the claims are not intended to require *de novo* crystallization or homology modeling without the benefit of the solved crystal structure, reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection of Claims 20-21, 23-24, 26-27, 34 and 36 under 35 U.S.C. §102(e) or 103

Applicants note with appreciation the Office's reconsideration and withdrawal of the previous rejections of the claims under 35 U.S.C. §102(e) or 103 over Tang *et al.*, U.S.

6,545,127. As acknowledged by the Office, the "inhibitor of the 3-D structure of Tang et al. is disclosed as being OM99-2, which appears to be distinct from the APP inhibitor of claim 12." However, the Office has maintained the rejection of claims 20-21, 23-34, 26-27, 34 and 36 under 35 U.S.C. §102(e) as being anticipated by, or in the alternative, as being obvious under 35 U.S.C. §103(a) over the Tang reference, alone or in combination with Bridges *et al.* (2006) *Peptides* 27:1877-1885.

Applicants submit that these rejections of claims 20-21, 23-34, 26-27, 34 and 36 over the Tang reference have been met by the amendments of the claims made herein. In particular, claim 20 (and its dependencies) have been amended herein to specify a complex of the BACE peptides (amino acids 58-447 of SEQ ID NO:1) and the particular APP inhibitor, which was acknowledged by the Office to be distinct from the inhibitors disclosed by Tang *et al.* Claims 34 and 36 have been amended to depend from claims 12 and 43, which are not subject to the present rejection.

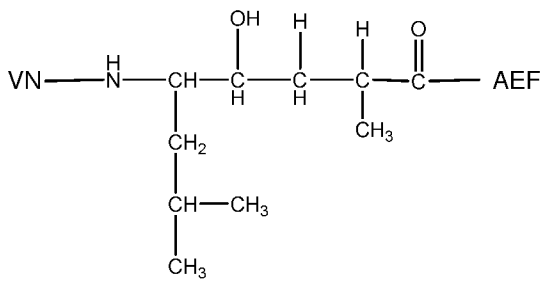
The Office cites to Bridges *et al.*, a publication dated at least five years after Applicants' filing date, as providing evidence contradicting Applicants' statements previously presented in support of the novelty and non-obviousness of the claims. From the outset, the state-of-the-art in 2006 at the time the Bridges reference published is much difference from 2000-2001 when the instant application was filed. Thus, Applicants question the evidentiary value of the Bridges reference, which has at least a five-year delay compared to the present application. Moreover, even if the Bridges reference is considered, the references merely notes that the structures discussed in Bridges are noted to be "similar" to the BACE1:MSP-1 structures discussed therein. Similarity does not mean the same. For purposes of 35 U.S.C. §102, the structures must be the same. As discussed in the previous Amendment and in more detail below, the differences in ligand structure, unit cell dimensions and angles necessarily show that the claimed three-dimensional structure and the structures of Tang are not the same. Similarly, the differences in the amino acid sequence of the BACE peptide and the particular APP inhibitor peptide used by Applicants compared to the complexes disclosed by Tang et al. provide significant structural differences not suggested by the prior art. These differences are described in more detail below.

Thus, reconsideration and withdrawal of the rejection of claims 20-21, 23-34, 26-27, 34 and 36 under 35 U.S.C. §102(e) is respectfully requested.

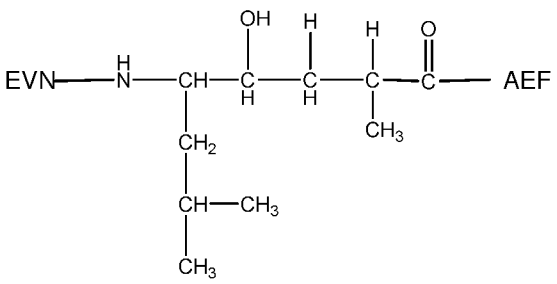
The Office has maintained the rejection of claims 12-16, 18-24, 26-27 and 33-36 under 35 U.S.C. §103(a) over the Tang reference in view of *In re Gulack*, 217 USPQ 401 (Fed Cir 1983). Applicants traverse this aspect of the rejection as applied to the claims, as amended herein. The claims, as presently pending, require the use in concrete steps of a specific three-dimensional representation of the structural coordinates of the complex of human BACE peptide consisting essentially of amino acids 58-447 of SEQ ID NO:1 and the particular BACE inhibitor having the sequence, SEVNStaVAEF (SEQ ID NO:3), wherein Sta is (S)-statine, neither of which is taught or suggested by the Tang reference. The human BACE sequence disclosed by Tang *et al.* includes amino acids Ala14 to Thr454 of human BACE, and thus includes amino acids 14-57 and 448-454, which are not present in the BACE three-dimensional structure disclosed and claimed in the instant application. The 49-amino acid difference between the BACE sequence used in the crystals disclosed by Tang *et al.* compared to the crystals of the present application leads to new and non-obvious three-dimensional structures of human BACE that would not have been expected based on the teachings by Tang *et al.*

In addition, the claims, as amended herein, require the use of the three-dimensional coordinates of the complex of the human BACE amino acid sequence described above and the particular BACE inhibitor having the sequence, SEVNStaVAEF (SEQ ID NO:3), wherein Sta is (S)-statine. The inhibitor specified in the claimed methods also differs from the inhibitor specified by Tang et al. in new and non-obvious ways. In particular, the Tang reference discloses a crystal structure of BACE (amino acids Ala14 to Thr454) bound to either OMP99-1 or OMP99-2.

Relevant portions of the structure of each of OMP99-1 and OMP99-2 are shown below based on the description of the Leu*-Ala isostere provided by Tang.



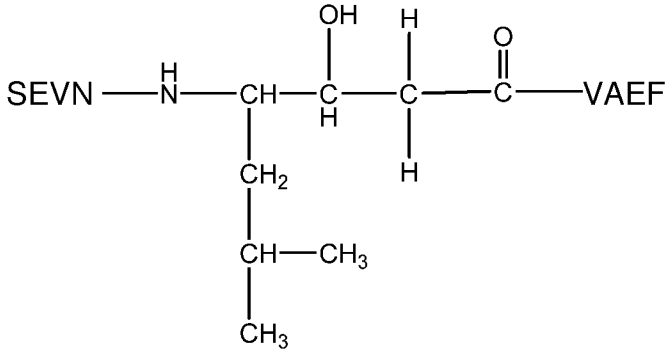
OMP99-1



OMP99-2

When the above structures of each of OMP99-1 and OMP99-2 are considered, OMP99-1 has seven amino acid residue equivalents (based on the presence of the number of HN-C_α-C=O or HN-C_α-C-OH backbone moieties) and OMP99-2 has eight amino acid residue equivalents with the Leu*-Ala isostere being two amino acid residue equivalents.

In contrast, the pending claims recite that the BACE peptide used in the three-dimensional representation consists essentially of the amino acid sequences of residues 58-447 of SEQ ID NO.1 and wherein the three dimensional structure comprises the relative coordinates of BACE according to Figures 1A-1EEE. It is noted that the ligand SEVN-Sta-VAEF is included in the coordinates in Figure 1. (See atoms 3062-3135). The structure of the SEVN-Sta-VAEF ligand is shown below and includes about ten amino acid residue equivalents.



The presence of the two additional amino acid equivalents would necessarily provide a different three-dimensional binding site due to the extra length. For example, the average C_α-C=O bond length is 1.52 Angstroms, the average bond length for O=C-NH is 1.33 Angstroms and the average bond length of HN-C_α is 1.45 Angstroms (or a total bond length of about 4.3 Angstroms for each additional amino acid equivalent). Assuming that the Sta and the Leu*-Ala isostere have about the same overall length, the presence of about two additional amino acid equivalents in the ligand of the claimed three-dimensional structure would provide a ligand that is at least about 8 Angstroms longer along the amino acid backbone than the ligands used in Tang.

Based on the differences in chain length, the three-dimensional structure of the binding site would be different when OMP99-1 or OMP99-2 is bound to BACE, as compared to when SEVN-Sta-VAEF is bound to BACE. This result is confirmed when the unit cell dimensions and

angles are considered for each of the structures. Tang discloses a unit cell having a=53.7, b-85.9 and c=109.2 with angles of α=90.0°, β=101.4° and γ=90.0° when OMP99-2 is bound to BACE. See Col. 32, Table 2 of Tang.

In contrast, the longer length of the ligand used to provide the claimed three-dimensional structure has a unit cell with dimensions of a=86.627, b=130.861 and c=130.729 with angles α= β= γ=90°. *See* last full paragraph of Section A of Example 1. Thus, the dimensions of the unit cell of the claimed structure are larger based, at least in part, on the use of a longer ligand. In addition, the angles of the unit cell of the claimed three-dimensional structure are all equal, whereas the angles of the unit cell of Tang are not all equal. It is improper to ignore these structural distinctions in determining whether the claimed subject matter is anticipated and/or obvious.

In addition to the longer length of the ligand used in the claimed structure and the differences in unit cell dimensions and angles noted above, the composition of the ligand of Tang differs chemically from the ligand used to provide the claimed three-dimensional structure. For example, Tang does not have the N-terminal serine group, which can form a hydrogen bond with residues in the binding pocket through its uncharged side chain hydroxy group.

The differences between the particular complex of the BACE peptide and the APP inhibitor as recited by the claimed methods (compared to the complex disclosed by Tang *et al.*) impose a new and non-obvious change in the screening process that ultimately leads to the synthesis and/or *in vitro* or *in vivo* selection of new candidate agents. For example, as shown by the Tang reference in column 22, OM99-1 and OM99-2 have identical amino acid sequences with the exception of an additional Glutamate residue present at the N-terminus of OM99-2, which is absent in OM99-1. When comparing the inhibition of BACE *in vitro* using these two inhibitors, OM99-1 had a Ki of 3x10-8M, whereas OM99-2 had a Ki of 9.58x10-9M (see Tang et al., columns 28-29). Thus, a single amino acid difference between OM99-1 and OM99-2 has a marked effect on its inhibitory activity. Therefore, the APP inhibitor of the presently claimed three-dimensional complexes, which is even longer than the inhbitors disclosed by Tang et al., would have been expected to have a more pronounced effect on the three-dimensional structure that would have led, in turn, to a marked effect on the activity of BACE. Thus, the structural information disclosed in Figures 1A-1EEE imparts a series of concrete steps that ultimate results in the physical screened agent. Such new and non-obvious methods alter the steps of the

computer program used in the *in silico* screen, which leads to the synthesis and/or *in vitro* or *in vivo* selection of new candidate agents. The structural coordinates of the APP binding site are not merely used for comparison of the structural coordinates of the candidate agent. The structural coordinates are in fact changed during the docking process of the candidate agent (see pages 28-29 of the Amendment filed on October 3, 2007, citing N. Claude-Cohen (1990) *J. of Med. Chemistry* 33(3):883-894, the substance of which is reiterated here). As the orientation of the candidate agent is adjusted, the three-dimensional coordinates of the APP-binding site are changed.

Therefore, based on the presence of different amino acids, the differences in the length of the ligands and the differences in the unit cell dimensions provided by the claimed three-dimensional structure, the claimed subject matter is different and non-obvious over the complexes disclosed by Tang et al. These characteristics impart a functionality by changing the processing steps of the computer program, changing the structural coordinates of the APP-binding site of BACE and the candidate agent, which ultimately impose a change in the screening process. Such structural information is not descriptive, as alleged by the Office, as it imparts a series of concrete steps having a functional relationship between the matter and the substrate. Accordingly, reconsideration and withdrawal of this rejection under 35 U.S.C. §103(a) is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, reconsideration is respectfully requested. This application should now be in condition for allowance; a notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an accompanying Deposit Account authorization, please charge any deficiency to Deposit Account No. 50/2762, referencing Attorney Docket No. W2025-701110.

Respectfully submitted,
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